VASOPRESSIN FORMULATIONS FOR USE IN TREATMENT OF HYPOTENSION

CROSS REFERENCE

This application is a continuation-in-part of U.S. application Ser. No. 15/426,693, filed Feb. 7, 2017, which is a continuation-in-part of U.S. application Ser. No. 15/289,640, filed Oct. 10, 2016, which is a continuation-in-part of U.S. application Ser. No. 14/717,877, filed May 20, 2015, which is a continuation of U.S. application Ser. No. 14/610,499, filed Jan. 30, 2015, each of which is incorporated herein by reference in its entirety.

BACKGROUND

Vasopressin is a potent endogenous hormone, responsible for maintaining plasma osmolality and volume in most mammals. Vasopressin can be used clinically in the treatment of sepsis and cardiac conditions, and in the elevation of patient's suffering from low blood pressure. Current formulations of vasopressin suffer from poor long-term stability.

INCORPORATION BY REFERENCE

Each patent, publication, and non-patent literature cited in the application is hereby incorporated by reference in its entirety as if each was incorporated by reference individually.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on May 26, 2017, is named 47956702504_SL.txt and is 5222 bytes in size.

SUMMARY OF THE INVENTION

In some embodiments, the invention provides a pharmaceutical composition comprising, in a unit dosage form: a) from about 0.01 mg/mL to about 0.07 mg/mL of vasopressin, or a pharmaceutically-acceptable salt thereof; and b) a polymeric pharmaceutically-acceptable excipient in an amount that is from about 1% to about 10% by mass of the unit dosage form or the pharmaceutically-acceptable salt thereof, wherein the unit dosage form exhibits from about 5% to about 10% less degradation of the vasopressin or the pharmaceutically-acceptable salt thereof after storage for about 1 week at about 60° C. than does a corresponding unit dosage form, wherein the corresponding unit dosage form consists essentially of: A) vasopressin, or a pharmaceutically-acceptable salt thereof; and B) a buffer having acidic pH.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a chromatogram of a diluent used in vasopressin assay.

FIG. **2** is a chromatogram of a sensitivity solution used in a vasopressin assay.

FIG. **3** is a chromatogram of an impurity marker solution used in a vasopressin assay.

FIG. **4** is a zoomed-in depiction of the chromatogram in FIG. **3**.

FIG. **5** is a chromatogram of a vasopressin standard solution.

FIG. **6** is a chromatogram of a sample vasopressin preparation.

FIG. **7** is a UV spectrum of a vasopressin sample.

FIG. **8** is a UV spectrum of a vasopressin standard.

FIG. **9** plots vasopressin stability across a range of pH as determined experimentally.

FIG. **10** illustrates the effects of various stabilizers on vasopressin stability.

FIG. **11** plots vasopressin stability across a range of pH at 25° C.

FIG. **12** plots vasopressin impurities across a range of pH at 25° C.

FIG. **13** plots vasopressin stability across a range of pH at 40° C.

FIG. **14** plots vasopressin impurities across a range of pH at 40° C.

FIG. **15** illustrates vasopressin impurities across a range of pH at 25° C.

FIG. **16** illustrates vasopressin impurities across a range of pH at 40° C.

FIG. **17** illustrates the effect of pH on vasopressin at 25° C.

FIG. **18** illustrates the effect of pH on vasopressin at 40° C.

FIG. **19** depicts the % LC of vasopressin formulations stored for 15 months at 25° C.

FIG. **20** below shows a diagram of a cap to be used on a vial described herein.

FIG. **21** depicts a stopper to be used in a vial described herein.

FIG. **22** shows a vial for use in storing a 10 mL vasopressin formulation described herein.

FIG. **23** shows the vasopressin assay results (represented as % label claim) of studies performed at 25° C. with upright storage.

FIG. **24** shows the vasopressin assay results (represented as % label claim) of the studies performed at 25° C. with inverted storage.

FIG. **25** shows the amount of Gly9-AVP when a 10 mL vasopressin formulation was stored at 25° C. in an upright position.

FIG. **26** shows the amount of Gly9-AVP when a 10 mL vasopressin formulation was stored at 25° C. in an inverted position.

FIG. **27** shows the amount of Glu4-AVP when a 10 mL vasopressin formulation was stored at 25° C. in an upright position.

FIG. **28** shows the amount of Glu4-AVP when a 10 mL vasopressin formulation was stored at 25° C. in an inverted position.

FIG. **29** shows the total impurities when a 10 mL vasopressin formulation was stored at 25° C. in an upright position.

FIG. **30** shows the total impurities when a 10 mL vasopressin formulation was stored at 25° C. in an inverted position.

DETAILED DESCRIPTION

Vasopressin and Peptides of the Invention.

Vasopressin, a peptide hormone, acts to regulate water retention in the body and is a neurotransmitter that controls circadian rhythm, thermoregulation, and adrenocorticotrophic hormone (ACTH) release. Vasopressin is synthesized as a pro-hormone in neurosecretory cells of the hypothalamus, and is subsequently transported to the pituitary gland for storage. Vasopressin is released upon detection of hyperosmolality in the plasma, which can be due to dehydration of the body. Upon release, vasopressin increases the permeability of collecting ducts in the kidney to reduce renal excretion of water. The decrease in renal excretion of water leads to an increase in water retention of the body and an